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(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Method of Stimulating Appetite

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(71) Same as inventor

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103 inven 8  
claim

Notice: This application is as filed and may therefore contain an  
incomplete specification.

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2095786

ABSTRACT OF THE DISCLOSURE

The present invention relates to a method for treating appetite disorders in a patient and in particular a method for the stimulation of appetite in a patient requiring appetite stimulation. The patient is peripherally administered an effective amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof. The invention also relates to a pharmaceutical formulation adapted for peripheral administration in a patient having an appetite disorder and to the use of growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof adapted for peripheral administration to treat patients with eating disorders and in particular to stimulate appetite in a patient requiring appetite stimulation.

2095786

- 17 -

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method for treating appetite disorders in a patient comprising peripherally administering to a patient an effective amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof.
2. A method for the stimulation of appetite in a patient requiring appetite stimulation comprising peripherally administering to a patient an effective appetite-stimulating amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof.
3. The method of claim 1 or 2 wherein said growth hormone-releasing factor is growth hormone-releasing factor (1-40), growth hormone-releasing factor (1-44), or growth hormone-releasing factor (1-29)NH<sub>2</sub>.
4. The method of claim 1 or 2 wherein said growth hormone-releasing factor is administered in a dose of between 0.01-10 µg/Kg body weight.
5. The method of claim 1 or 2 wherein said growth hormone-releasing factor is administered to a patient with anorexia nervosa.
6. The method of claim 1 or 2 wherein said growth hormone-releasing factor is administered parenterally, orally, topically, rectally, locally, or by inhalation.
7. The method of claim 1 or 2 wherein said growth hormone-releasing factor is intravenously administered.
8. The method of claim 2 wherein the growth

2095786

- 18 -

hormone-releasing factor is administered to a patient suffering from loss of appetite due to aging, general fever, or cancer, illness due to damage or lesion of the region of the brain controlling appetite, appetite dysfunctions in conjunction with dwarfism or short stature.

9. The method of claim 1 wherein the patient has bulimia.

10. A pharmaceutical formulation adapted for peripheral administration in a patient having an appetite disorder comprising an effective amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof, and a pharmaceutically acceptable carrier therefor.

11. A pharmaceutical formulation adapted for peripheral administration in a patient requiring appetite stimulation comprising an effective appetite-stimulating amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof, and a pharmaceutically acceptable carrier therefor.

12. The pharmaceutical formulation of claim 10 or 11 which is adapted for parenteral, oral, topical, rectal, local or inhalation administration.

13. The pharmaceutical formulation of claim 10 or 11 which is adapted for intravenous administration.

14. The pharmaceutical formulation of claim 10 or 11 wherein the concentration of growth hormone-releasing factor is in the range of 0.01-10.0 µg/Kg body weight.

15. The pharmaceutical formulation of claim 10 or 11

2095786

- 19 -

wherein said growth hormone-releasing factor is growth hormone-releasing factor (1-40), growth hormone-releasing factor (1-44), or growth hormone-releasing factor (1-29)NH<sub>2</sub>.

16. The pharmaceutical formulation of claim 11 for use in treating a patient who suffers from anorexia, loss of appetite due to aging, general fever, or cancer, illness due to damage or lesion of the region of the brain controlling appetite, appetite dysfunctions in conjunction with dwarfism or short stature.

17. The pharmaceutical formulation of claim 10 for use in treating a patient with bulimia.

2095786

- 1 -

Title: Method of Stimulating Appetite

FIELD OF THE INVENTION

The invention relates to methods and formulations for affecting appetite.

BACKGROUND OF THE INVENTION

Anorexia nervosa (AN) is a serious psychiatric disorder with a high morbidity and mortality rate. Psychological symptoms associated with AN usually precede extreme dieting, weight loss and amenorrhea. Normal eating patterns are lost as the body's usual response to hunger is overruled. Seriously underweight individuals require several months of intensive medical treatment to promote weight gain and normal eating. To date, the numerous attempts at using various drug therapies to stimulate appetite in AN patients have not demonstrated significant benefits (Kennedy SH et al, in The Biology of Feast and Famine (1992) Chapter 20: New Drugs, New Directions, pp 341-56).

Neuropeptides which have been reported to stimulate eating following central injection include somatostatin, opioid peptides, and the pancreatic peptides neuropeptide Y and neuropeptide YY (Feifel D and Vaccarino FJ (1990) Brain Research 535:189-94; Levine AS and Morley JE (1982) Pharmacology, Biochemistry and Behaviour 16:897-902; Lotter EC et al (1981) J. Compar. and Physiolog. Psychol. 95:278-87; Baile CA et al (1986) Physiological Reviews 66(1):172-234; Morley JE et al (1987) Am. J. Physiol. 252:R599-609).

None of the abovementioned neuropeptides stimulates eating following peripheral injection and in fact, there is a tendency towards decreased eating following peripheral injection. The ineffectiveness of peripherally-

2095786

- 2 -

administered peptides in producing behavioral effects is usually attributed to their difficulty in crossing from peripheral circulation to brain tissue, through the blood brain barrier.

Growth-hormone releasing factor (GRF) is a peptide which has potent endocrine action and stimulates growth hormone (GH, somatotropin) release from the anterior pituitary gland through the hypophysial- portal blood system.

Cacabelos et al (Cacabelos R et al (1988) Acta Endocrinol. 117:295-301) reported that intravenous administration of 100 µg GRF(1-44)NH<sub>2</sub> in patients with early onset senile dementia of the Alzheimer type elicited a marked plasma GH response. Mental performance and behaviour were also evaluated using a number of tests for mental assessment.

The results of recent studies in animals have suggested that in addition to its endocrine effects, GRF has motivationally relevant behavioral effects. Vaccarino et al were the first to demonstrate a behavioral role for centrally (intracerebroventricularly, or i.c.v.) injected GRF (Vaccarino FJ et al ((1985) Nature 314:167-8). They demonstrated that GRF, in picomole doses, stimulated food-intake in food-deprived male Wistar rats. Other studies demonstrated the same effect in free-feeding rats, and further showed that high (nanomole) doses of the peptide do not stimulate food intake and may even cause a depression of feeding behaviour (Vaccarino FJ et al (1988) Peptides-NY-9: Suppl 1: 35-38; Imaki T et al (1985) Brain Res. 340:186-88).

Tanaka et al studied the effects of centrally administered GRF in food-deprived female Sprague-Dawley rats. They found that GRF, in doses of 50 or 100 picomol significantly stimulated food intake as compared with controls, while doses of 0.5 and 1.0 nanomol significantly

2095786

- 3 -

decreased food intake (Tanaka Y et al(1991) Brain Res. 558:273-9). Synthetic human GRF (1-44) has also been reported to stimulate feeding in non-lactating ewes (Riviere P. & Bueno L. ((1987), Physiol. Behav. 39:347-50).

Vaccarino et al have shown that central administration of a physiologically inactive peptide analog of GRF produced no effect on feeding. Vaccarino et al have also demonstrated that i.c.v. GRF administration in doses lower than those required to stimulate GH release stimulated food intake without causing general behavioral arousal (Vaccarino FJ et al (1985) Nature 314:167-8; Vaccarino FJ et al (1988) Peptides [Suppl 1] 9: 35-38; Feifel D and Vaccarino FJ (1989) Behav. Neurosci. 103: 824-30). They also demonstrated that peripheral injections of GRF, in doses effective centrally, had no effect on food intake (Vaccarino F.J. et al (1985) Nature 314: 167-8). Rats administered i.c.v. GRF have also been found to have increased motivation to work for food (Feifel D and Vaccarino FJ (1990) Prog. Neuro-Psychopharmacol. & Biol. Psychiat.14:813-20). Centrally administered anti-GRF antibodies have been found to attenuate food intake without affecting other behaviours (Vaccarino FJ et al (1990) Ann NY Acad. Sci. 579:227-32).

Mapping studies have indicated that the suprachiasmatic nucleus/medial preoptic area (SCN/MPOA) of the hypothalamus, which receives GRF-containing terminals, is a critical site for GRF-induced feeding (Vaccarino FJ and Hayward M (1988) Regul. Pept. 21:21-8; Dickson and Vaccarino (1990) Am. J. Physiol. 259:R651-7).

The role of GRF in the regulation of eating in humans is not known. Abnormalities in the responsiveness of GH to GRF have been associated with eating disorders (Kennedy SH et al (1992) in The Biology of Feast and Famine, chapter



2095786

- 4 -

20 - New Drugs, New Directions, pp341-356). While obese individuals show a diminished GH response to GH-releasing challenges (including GRF), AN individuals show an exaggerated GH response (Williams T et al (1984) NEJM 311:1403-7; Brambilla F et al (1987) Psychiatry Res. 20:19-31; (1989) Biol. Psychiatry 25:256-64; Rolla M et al (1990) Biol. Psychiatry 27: 215-222; Tamai H et al (1990) J. Clin. Endocrinol. Metabol. 70: 738-41). However, others have failed to replicate these findings in AN (Casanueva FF et al (1987) Clin. Endocrinol. 27: 517-23, and Merriam GR et al (1985) Neuroendocrinol. Lett. 7: 102).

It has been reported that the response of GH to GH-releasing stimuli including GRF in individuals with AN does not correlate with either the duration of the illness nor the degree of weight loss (Brambilla F et al (1989) Biol. Psychiatry 25: 256-64). However, the response can be normalised with increased caloric intake (Rolla M et al (1990) Biol. Psychiatry 27: 215-222).

#### SUMMARY OF THE INVENTION

The present inventors have found that growth hormone-releasing factor affects appetite when administered to a patient. In particular, the present inventors have found that peripherally-administered GRF (1 µg per kg body weight) stimulates appetite in anorexia nervosa patients and decreases appetite in control subjects. Anorexia patients reported increased hunger and ate more following administration of GRF while control subjects had a decreased food intake following GRF administration. Peripherally administered GRF was also found to reduce binging in Bulimia patients.

Broadly stated the invention relates to a method for treating eating disorders comprising administering an effective amount of a growth hormone-releasing factor or

2095786

- 5 -

a pharmaceutically acceptable derivative, analog, salt or complex thereof. The invention also contemplates a pharmaceutical formulation adapted for peripheral administration in a patient having an appetite disorder comprising an effective amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof, and a pharmaceutically acceptable carrier therefor.

An embodiment of the present invention relates to a method for the stimulation of appetite in a patient requiring appetite stimulation comprising peripherally administering to a patient an effective appetite-stimulating amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof.

The invention also relates to a pharmaceutical formulation adapted for peripheral administration in a patient requiring appetite stimulation comprising an effective appetite-stimulating amount of a growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof, and a pharmaceutically acceptable carrier therefor.

The invention also relates to the use of growth hormone-releasing factor or a pharmaceutically acceptable derivative, analog, salt or complex thereof adapted for peripheral administration to treat an appetite disorder in a patient and in particular, to stimulate appetite in a patient requiring appetite stimulation.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Further details of the invention are described below with the help of the examples illustrated in the accompanying drawings in which:

Figure 1 is a bar graph showing food intake in controls

2095786

- 6 -

who have been administered GRF and a placebo;

Figure 2 is a bar graph showing macronutrient intake in controls who have been administered GRF and a placebo;

Figure 3 is a graph showing macronutrient intake in a patient who was administered GRF and a placebo;

Figure 4 is a graph showing macronutrient intake in a patient who was administered GRF and a placebo;

Figure 5 is a graph showing % change for protein, fat, and carbohydrate intake during placebo and GRF treatment in anorexia patients, anorexia and bulimia patients, and normals; and

Figure 6 is a graph showing % change for total caloric intake during placebo and GRF treatment in anorexia patients, anorexia and bulimia patients and normals.

#### DETAILED DESCRIPTION OF THE INVENTION

As discussed above, the present invention relates to methods and formulations for treating appetite disorders using GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof. In one embodiment of the invention a method for the stimulation of appetite in a patient requiring appetite-stimulation is provided comprising peripherally administering to a patient an effective appetite-stimulating amount of GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof; to pharmaceutical formulations which are adapted for peripheral administration containing GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof; and, to the use of GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof to treat appetite disorders, in particular to stimulate appetite in a patient requiring appetite

2095786

- 7 -

stimulation.

The term "appetite" used herein means an appetitive effect during eating and/or expression of an appetitive effect, including increased food intake.

GRF that may be used in the method, composition and use of the invention includes the fully bioactive, 44 amino acid peptide from human pancreatic tumor (hpGRF) isolated and characterized by Guillemin R. et al ((1982) Science 218:585); native human hypothalamic GRF (hGRF) (Böhlen et al., (1983) Biochem. Biophys. Res. Comm. 114:930-36; Ling N. et al (1984) Proc. Natl. Acad. Sci. U.S.A. 81:4302); GRF (1-40) and GRF (1-44) (Rivier J. et al Nature (1982) 300:27 and Guillemin R. et al (1982) Science 218:585); GRF (1-29)-NH<sub>2</sub> (Rivier J. et al Nature (1982) 300:27); recombinant GRF; synthetic peptides thereof, pharmaceutically acceptable derivatives, analogs, salts or complexes thereof; and biologically active fragments of GRF displaying growth hormone releasing activity. Preferably [Nle<sup>27</sup>]GRF (1-29)NH<sub>2</sub>, most preferably Somatrel® available from Ferring Inc., Willowdale, Canada is used in the present invention. Analogs of GRF such as the analogs described by Lance et al. in Biochem, Biophys. Res. Comm. 119, 265-272 (1984), Rivier et al. in U.S. Patent No. 4,518,586, in U.S. Patent NO. 4,428,190 and Felix et al. in Canadian Patent No. 1,270,598 may be used in the present invention. Porcine, bovine, ovine, or caprine GRF may be used in the present invention.

The method and composition of the invention may be used to treat humans which require stimulation of appetite. In particular, the method and composition may be used to stimulate appetite in humans suffering from anorexia, most particularly anorexia nervosa, loss of appetite due to aging, general fever or underlying diseases such as cancer, and illness due to damage or lesion of the region

2095786

- 8 -

of the brain controlling appetite. The method and composition may also be used to stimulate appetite in children with appetite dysfunctions, in particular appetite dysfunctions in conjunction with conditions such as dwarfism or short stature. The method and composition of the invention may also be used to normalize appetite in patients with conditions such as bulimia.

The GRF in appropriate pharmaceutical formulation may be administered orally, topically, rectally, parenterally, locally or as an inhalant. The pharmaceutical formulations are therefore in solid or semisolid form, for example pills, tablets, creams, gelatin capsules, capsules, suppositories, soft gelatin capsules, gels, membranes, tubelets. For parenteral use, those forms for intramuscular, subcutaneous or intraperitoneal administration can be used, or forms for infusion or intravenous injection can be used, and can therefore be prepared as solutions of the active compound or as powders of the active compound to be mixed with one or more pharmaceutically acceptable excipients or diluents, suitable for the aforesaid uses and with an osmolarity which is compatible with the physiological fluids. For local use, those preparations in the form of creams or ointments for topical use or in the form of sprays should be considered; for inhalant uses, preparations in the form of sprays, for example nose sprays, should be considered.

The pharmaceutical formulations can be prepared by per se known methods for the preparation of pharmaceutically acceptable formulations which can be administered to patients, and such that an effective amount of the active substance, preferably an appetite stimulating quantity of the active substance, is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack

2095786

- 9 -

Publishing Company, Easton, Pa., USA 1985).

On this basis, the pharmaceutical compositions include, albeit not exclusively, solutions of a growth hormone-releasing factor or derivatives, or analogs, salts or complexes thereof in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

An effective amount of GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof is the minimum dose of GRF adequate to produce the desired appetite effect. An effective appetite-stimulating amount of a GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof is the minimum dose of GRF adequate for appetite stimulation. The dose of GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof will depend on such parameters as the desired effect, the chosen route of administration, and on the body weight and constitution of the patient. For the method according to the invention in humans, for example, the doses of GRF or a pharmaceutically acceptable derivative, analog, salt or complex thereof range from 0.01 to 10.0 µg per kilogram body weight, preferably 0.1 to 1.0 µg per kilogram body weight.

The following non-limiting example is illustrative of the present invention:

EXAMPLE

The effect of intravenous GRF on food intake, macronutrient selection, and perceptions of food preference in anorexia nervosa and control patients under double blind placebo controlled conditions was studied. The Structural Clinical Interview for DSM III(R) (Spitzer et al 1988) was administered for patient (SCID-P) and for

2095786

- 10 -

control assessment (SCID-NP) by a trained research assistant, who also administered the Hamilton Rating Scale for Depression (Hamilton 1960 J. Neural Neurosurg Psychiatry 23: 56-62) to both groups. The self report Eating Disorder Inventory (Garner et al 1983 Eat Dis 2:15-34) and Eating Attitudes Test (Garner et al 1982 Psycho Med 12:871-878) was also given to all subjects, as was the MEQ to obtain patient and control profiles.

Female patients, admitted to the Inpatient Eating Disorder Unit at the Toronto General Hospital who met DMS III(R) criteria for anorexia nervosa and who were free of psychotropic medication for at least 2 weeks were selected as eligible anorexia nervosa patients. The presence or absence of major depression and concurrent bulimia nervosa were noted for statistical evaluation but were not exclusion criteria. Female control subjects were required to be free from major psychiatric disorders, according to the SCID-NP and to be drug free for at least the previous 2 weeks.

A standard lunch which offered food choices from predominantly protein, carbohydrate and fat sources was provided and supervised by a physician. Table 1 is list of the foods provided. Both total caloric intake and macronutrient selection were calculated following meal completion. Perceptions of food preference were assessed during and after the study using a Motivation to Eat Questionnaire (MEQ), a series of visual analog scales on which the subject rates subjective feelings of hunger and satiety.

The meal was presented twice in a two week period and was preceded by insertion of an i.v. catheter with a two-way lock into the subject's arm of choice. Into this was injected either 1 ml/100 kg body weight of saline or [Nle<sup>27</sup>]GRF(1-29)NH<sub>2</sub> (1 µg per kg body weight (100 µg/ml)

- 11 -

Somatrel® from Ferring Inc., Willowdale, Ontario) in saline allocated in random order.

Blood samples for GH were drawn at the times indicated in Table 2 during the study. MEQs were also completed as outlined above. On each occasion patients were presented with the same lunch tray in the same dining room for 60 minutes. The following week the alternative injection was given and the study repeated. Table 2 summarizes the study protocol.

Patients were asked to eat freely under observation. Since meal supervision is standard practice for all AN patients from the time of admission, it was unlikely to alter their behaviour. It is also noted that previous eating studies, including those in which bulimic subjects are free to binge eat, have been carried out successfully with an intravenous line in-situ.

Two out of 4 AN patients studied reported increased hunger and ate more following GRF treatment (Figures 3 and 4). GRF was found to decrease food intake in normal subjects (Figures 1 and 2, and Table 3). The stimulatory affect in AN patients is particularly significant in light of the inhibitory effect found in normal subjects. The appetitive effect of GRF in AN patients suggest that they responded to GRF in a low dose manner, unlike normals, who responded in a high dose manner to the same dose. These results are consistent with a role of GRF in human eating regulation. Also, they provide evidence that GRF augmentation may be therapeutic in AN patients and that AN patients have an underactive GRF-eating system compared to normals.

Additional patients were studied using the above described protocol. In total, four anorexia nervosa patients, 4 mixed anorexia nervosa and bulimia patients, and 8 normals were studied. The data representing the averages of each



2095786

- 12 -

of these groups is shown in Figures 5 and 6. The present inventors have also observed that GRF administration decreased bingeing in the bulimia patients. Thus, GRF appears to be normalizing appetite in the anorexia and bulimia patients.

The present invention has been described in detail and with particular reference to the preferred embodiments; however, it will be understood by one having ordinary skill in the art that changes can be made thereto without departing from the spirit and scope thereof.

2095786

- 13 -

Table 1

Contents of Buffet Lunch

Schneiders "Life Style" Meats - Turkey (6 slices)  
- Ham (6 slices)  
- Bologna (6 slices)

Dempster's Bread - white (6 slices)  
- whole wheat (6 slices)

Cheese (225 g pkg.)

Mayonnaise (2 x 35 g containers)

Butter (2 x 35 g containers)

Fruit (1 apple + 1 pear)

Dessert: 5 oreo/5 oatmeal/5 chocolate chip cookies

Beverages: 2% milk (250 ml)/apple juice (250 ml)/  
orange juice (250 ml)

2095786

- 14 -

Table 2

Time	Item
11:29	Motivation to Eat Questionnaire
11:30	Insertion of Intravenous Line
12:00	Motivation to Eat Questionnaire
12:15 #1 Baseline	5 ml sample for GH
12:29	Motivation to Eat Questionnaire
12:30 #2 Baseline	5 ml sample for GH
12:31	1 ml saline <u>or</u> saline/GRF into IV
12:44	Buffet style lunch presented
12:44	Motivation to Eat Questionnaire
12:45 #3	5 ml sample for GH Start to eat <u>after</u> # 3 sample drawn
1:00 #4	5 ml sample for GH
1:15 #5	5 ml for GH
1:29	Motivation to Eat Questionnaire
1:30 #6	5 ml sample for GH
1:44	E n d o f M e a l Questionnaire**
1:45 #7	5 ml sample for GH
1:45	Food tray is removed
1:45	End of study

Table 2 cont'd

\*\* The end of meal questionnaire is also administered when the subject has finished eating in cases where meal termination occurs before 1:45.

1. Non-patient subjects came in for breakfast at 8:00 am.
2. Lunch time food trays stayed throughout the study (even if subject reported finishing meal). When subject felt that she had completed the meal, she filled out end of meal questionnaire.
3. If subject continued to eat after the end of meal questionnaire, she noted the time of this additional eating at the bottom of the end of meal questionnaire.

2095786

- 16 -

Table 3

	<u>GRF EFFECTS IN NORMALS</u>		
	Vehicle	GHRH	p<0.05
T o t a l Calories:	1143	793	*
P r o t e i n (g)	46	34	*
Fat (g)	47	34	*
c a r b o - hydrates (g)	141	95	*
T o t a l Solids:	891	628	*
P r o t e i n (g)	37	29	-
Fat (g)	42	30	*
C a r b o - hydrates (g)	95	65	*
Percentage Proteins	16	18	
Fat	37	37	
C a r b o - hydrates	50	49	

# FOOD INTAKE IN NORMALS

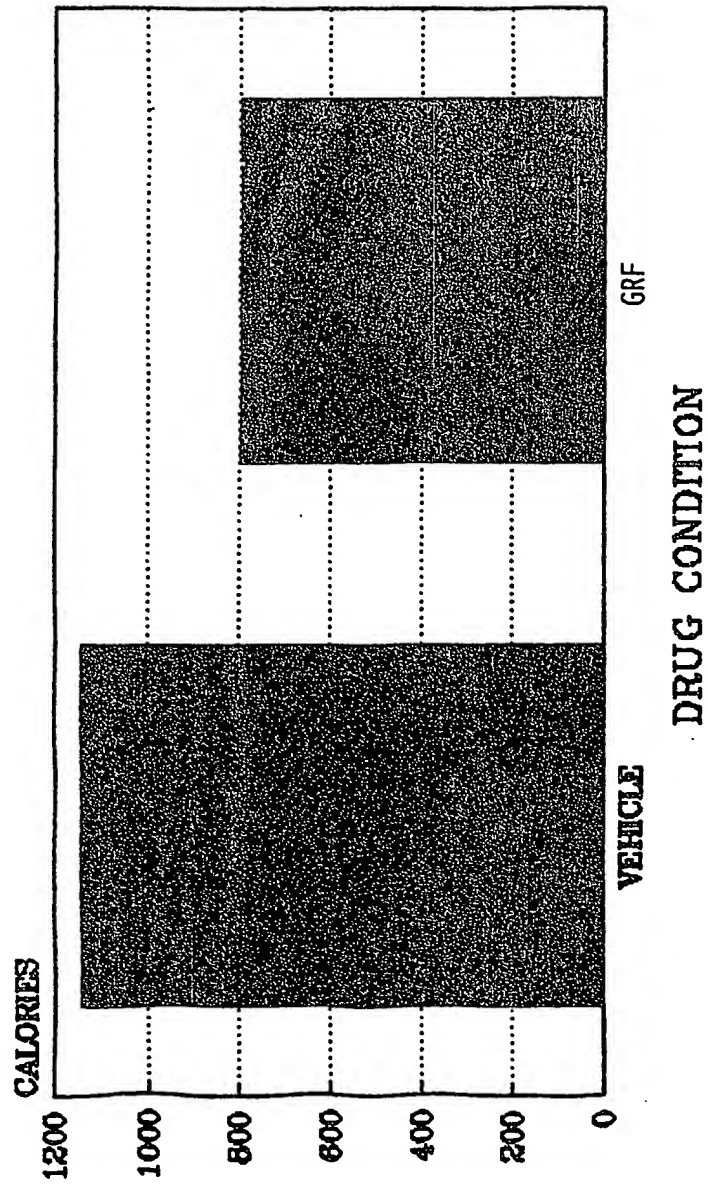


FIGURE 1



## FOOD INTAKE IN NORMALS

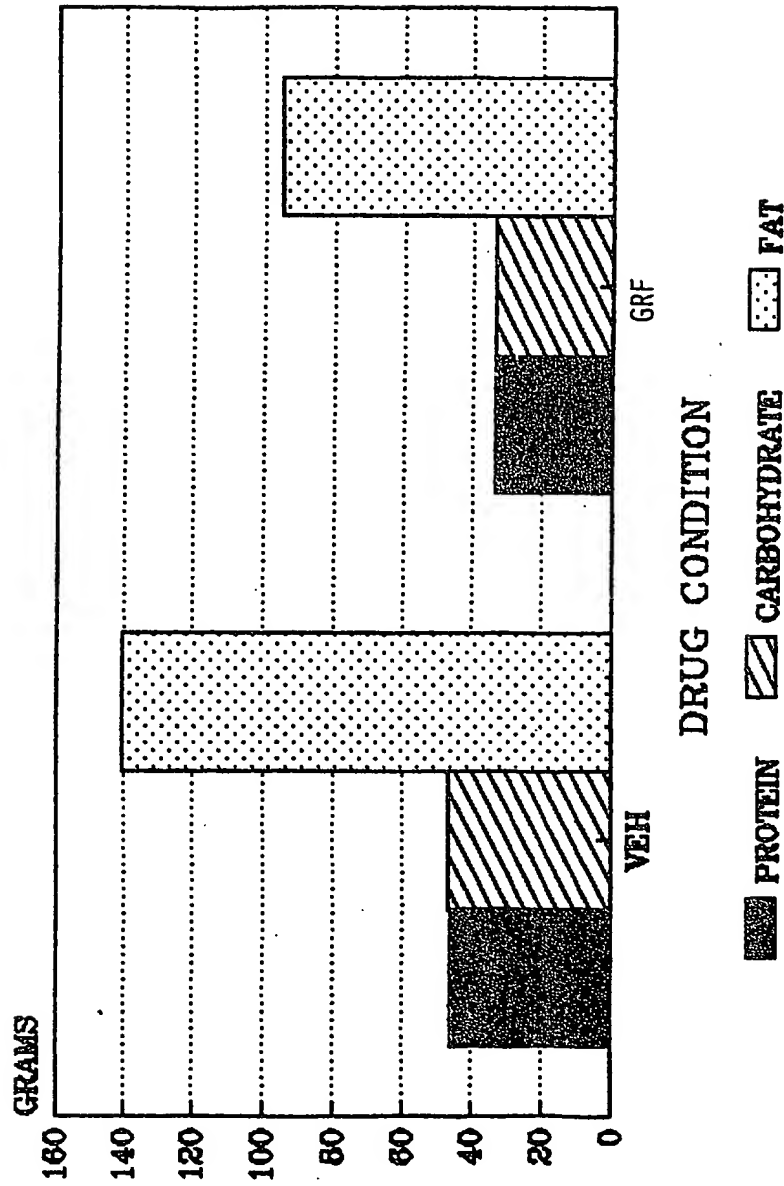


FIGURE 2

## FOOD INTAKE: PATIENT 1

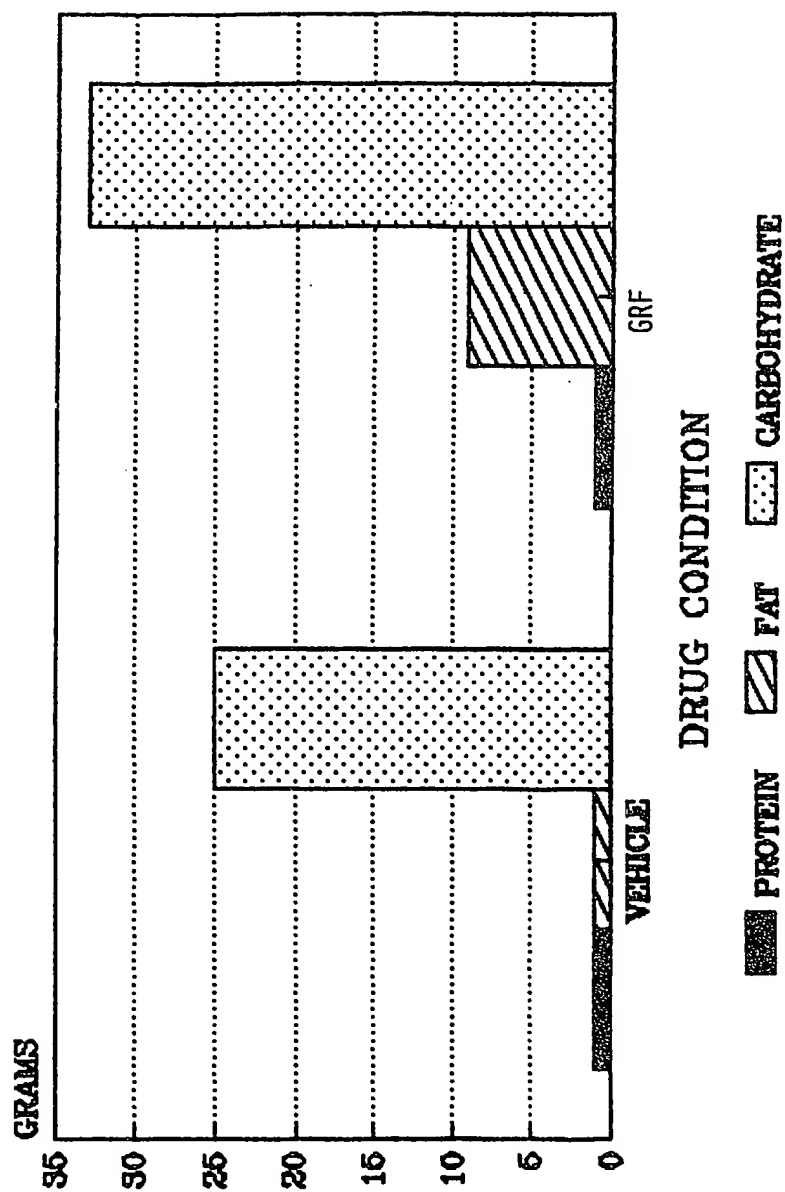


FIGURE 3



# FOOD INTAKE: PATIENT 2

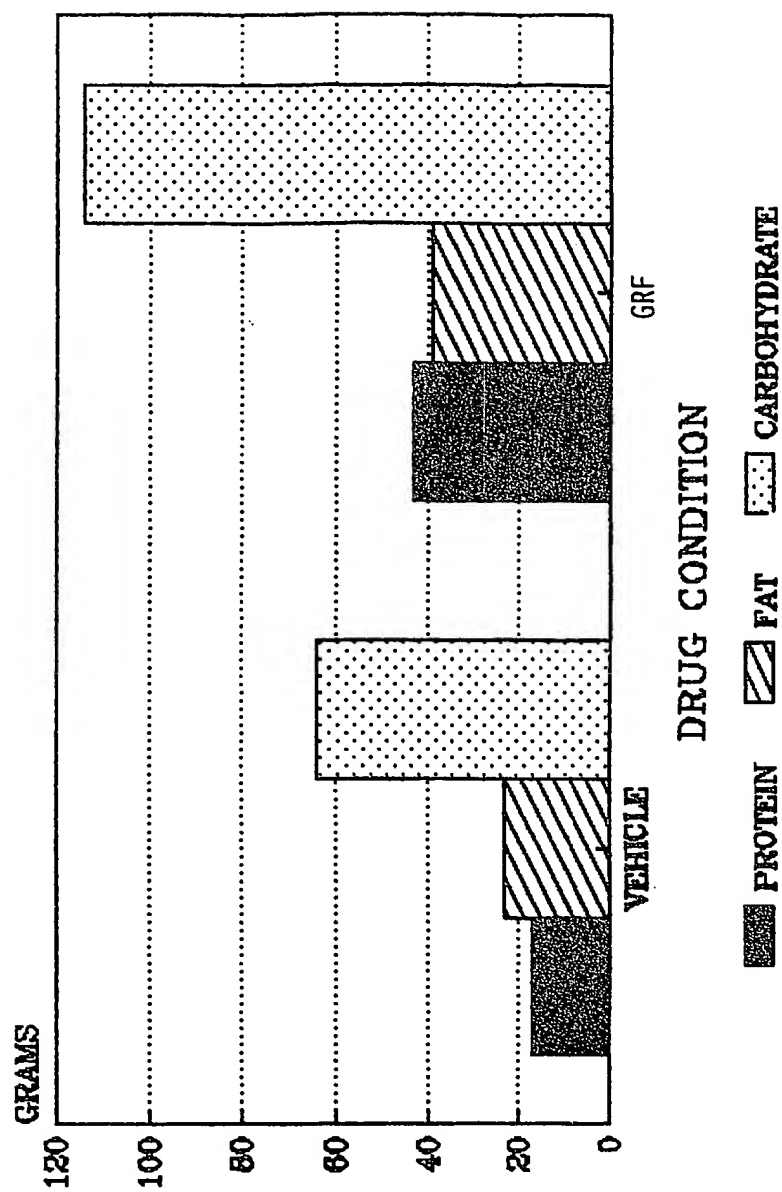


FIGURE 4

2095786

# % CHANGE FOR PROTEIN, FAT AND CARBOHYDRATE INTAKE DURING PLACEBO AND GRF FOR EACH DRUG CONDITION

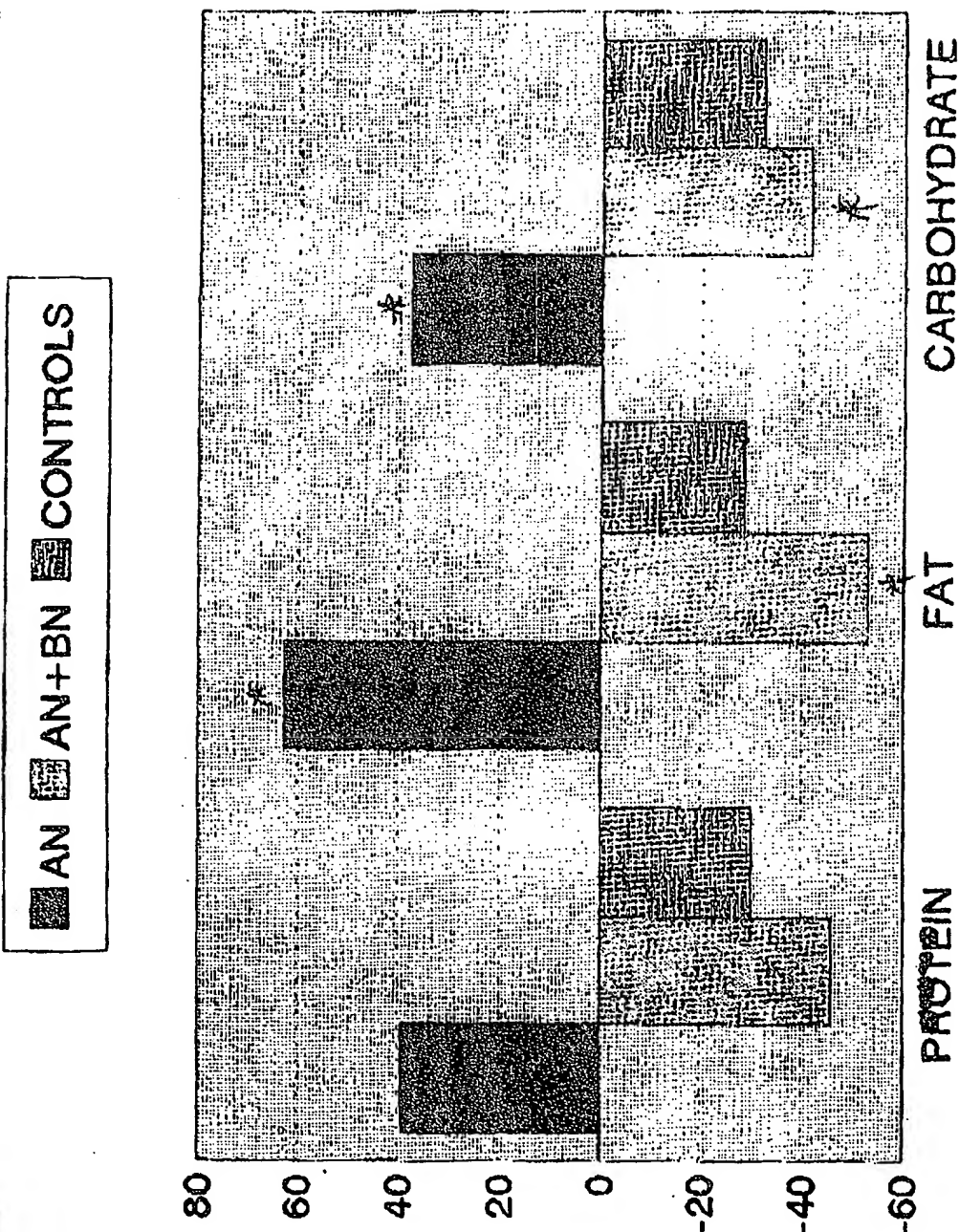


FIGURE 5

% CHANGE FOR TOTAL CALORIC INTAKE DURING PLACEBO AND GRF  
FOR EACH DRUG CONDITION

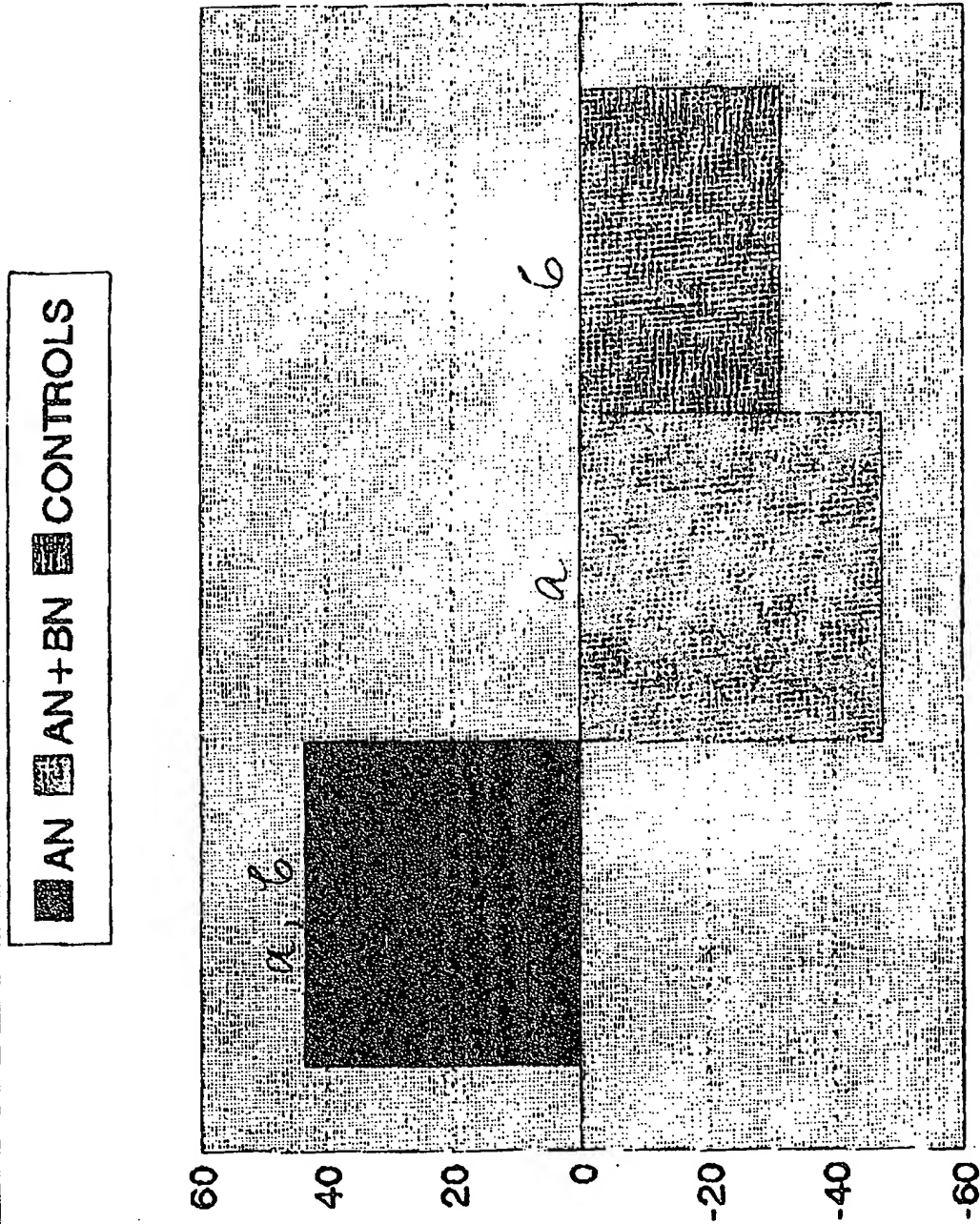


FIGURE 6